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The Lederle Bulletin

BOSTON MEDICAL
OCT 4 1924
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A concise presentation of authoritative information concerning the practical application and clinical value of biological therapy.

Published by

LEDERLE ANTITOXIN LABORATORIES
511 FIFTH AVE. NEW YORK CITY

September 1924

spite of such efficient treatment, this does not prevent spread of the disease. Individual antirabic treatment will not prevent rabies in a community. If the disease is to be eradicated, rabies must be prevented in the dog.

There are, however, but few preventive measures that can be adopted for controlling the spread of rabies. These include (1) the killing of stray and ownerless dogs, (2) quarantining and prohibiting dogs from running at large, and (3) muzzling. The enormous area to be policed in the United States prevents the universal application of such measures and they have, accordingly, failed to achieve the purpose for which they were intended. The PASTEUR treatment has never been used to any great extent in protecting dogs, largely because of its expense and time-consuming nature.

If, however, there was a prophylactic vaccination that could be applied to healthy dogs and which would be as effective as phophylactic vaccination against smallpox, there would be a good possibility of eradicating the disease. Until recently, no method of antirabic treatment ever suggested was practical for the purpose of protecting all dogs in a given locality before they become exposed to the disease. In common with its use in man, antirabic treatment for animals has been given after the animal has been bitten by a rabid animal.

An important advance now seems to have been made. Two Japanese investigators working at the Kitasato institute for Infectious Diseases in Tokyo, found it possible to confer immunity on healthy dogs by a single injection of vaccine. In the course of their experiments 500 dogs were vaccinated. No vaccination losses occurred, nor were there any dogs that contracted the disease. Subsequently 31,307 dogs were vaccinated in Tokyo and vicinity with the result that in only one case did the vaccination fail in producing sufficient immunity against natural exposure. Although it was not possible to vaccinate all dogs in the district, yet vaccination brought about a 75 per cent reduction in the number of cases of rabies, and the disease occurred only in those dogs which had not been vaccinated. In a more recent report by one of the Japanese investigators, the results are presented of 104,629 preventive inoculations of dogs against rabies in Tokyo and Yokohama and their environs. It is shown that only 41 of the inoculated dogs developed rab-

ies; while 1,699 of the non-vaccinated dogs contracted the disease, notwithstanding the fact that the non-vaccinated group represented only one-third of the total dog population.

These investigations were first brought to the attention of scientific workers in this country by a review which appeared in *The Journal of the American Medical Association* for June 18, 1921. Stimulated by these investigations, EICHHORN and LYON conducted experiments in the LEDERLE ANTITOXIN LABORATORIES and undertook to test the degree of immunity actually produced in dogs by a single vaccination. Their results confirmed those of the Japanese workers and are most encouraging. Their experiments, published in full in the *Journal of the American Veterinary Medical Association* for April, 1922, and March, 1924, justify the conclusion that dogs vaccinated by the one injection method, using a specially prepared fixed rabies virus, are protected against large doses of street virus. This method offers a promising opportunity of controlling, if not eventually eradicating, the disease.

The investigations of EICHHORN and LYON made it possible for Canine Rabies Vaccine (Lederle), One Injection Method, to be introduced in America in August, 1921. During the past three years, this product has been extensively used. Statistical data gathered from its use shows that more than 100,000 dogs have been vaccinated by this method in the United States; and the available reports show that all have been protected against the disease for a period of one year. Compulsory vaccination of all dogs in localities where the disease is prevalent has been adopted by some municipalities and States. Both local and State Boards of Health are recognizing the possibility of eradicating rabies by vaccination with the one injection method.

Relation of the Dick Test to Scarlet Fever

AT the Boston City Hospital, practical application of the DICK test was made in a series of 301 cases. The technic adopted by the DICKS was used, namely, an intracutaneous injection of 0.1 cc of the DICK scarlet fever toxin, properly diluted, was made on the anterior surface of the forearm.

Positive reactions began to appear as a circular area of erythema in about six hours. This gradually increased and reached a maximum intensity with swelling, redness and sometimes tenderness in 18 to 24 hours after the injection. In 48 hours the swelling had subsided and the color faded to a faint yellow. One week later, the area showed desquamation in several instances.

All convalescent scarlet fever patients gave negative reactions. Three patients acutely ill with scarlet fever gave slightly positive reactions but negative reactions in their convalescent stage two weeks later. BRANCH and EDWARDS in this series obtained 40 per cent positive reactions as compared to 41.6 per cent reported by the DICKS. The authors believe that the DICK test apparently has a specific relationship to immunity to scarlet fever.

Intra Cutaneous Tuberculin Test

PEDIATRICIANS have for some time been interested in the determination of a tuberculous infection through the use of the intracutaneous test of Mantoux.

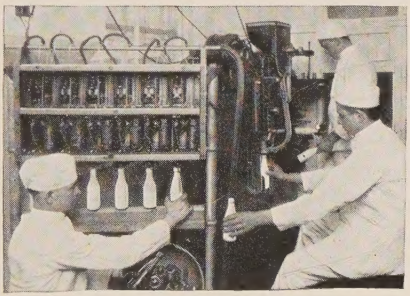
It is preferred by physicians on account of the greater reliability attending its application than is observed with the Von Pirquet method of testing.

The New York City Department of Health became interested in the subject and DR. KRUMWIEDE has prepared an outfit in a form similar to that in which the Schick Test is now provided, which has the advantage of being readily available in the physician's office and permits its very wide application.

The Tuberculin used for this test is Tuberculin O. T. The LEDERLE ANTITOXIN LABORATORIES are prepared to supply this tuberculin in an outfit convenient for office use.

The Manufacture of Bacillus Acidophilis Milk (Lederle)

MILK positively sterilized by steam pressure is used for the development of sufficient seed culture of Bacillus Acidophilus for the mass inoculation of the large batches of Bacillus Acidophilus Milk (Lederle) which are sterilized and incubated in jacketed glass-lined steel tanks, especially constructed for the purpose. The milk in the glass-lined tanks is sterilized by steam pressure and then cooled by water jacket to incubator temperature. While at this temperature, the milk in the tanks is inoculated with the seed culture of Bacillus Acidophilus whose purity has been established by agar plates and by microscopic examination. During the growth of the culture in the milk tanks, the degree of growth is determined by titrations for acidity which are made at various periods.



Filling, Capping and Labeling Bacillus Acidophilus Milk (Lederle)

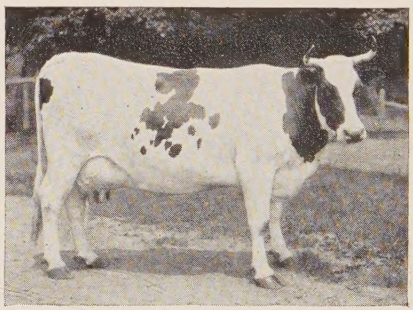
Filling and Storage

The filling of Bacillus Acidophilus Milk (Lederle) is carried out by means of specially designed apparatus which insures the delivery of the milk into sterile bottles without its being exposed to the air or anything else which could contaminate it. The filled bottles are immediately closed and sealed with sterile caps, after which the bottles are labeled, packed stored in a refrigerator and thoroughly chilled.

Final Bacteriological Studies

Every lot of Bacillus Acidophilus Milk (Lederle) is examined by the microscopic study of smears and de-

veloped agar plates to determine the purity of the culture and the approximate count of living Bacillus Acidophilus in each cubic centimeter of the milk. Bottles of Bacillus Acidophilus Milk (Lederle) are taken from the packed stock which is ready for distribution and dilutions of 1:100, 1:10,000 and 1:1,000,000 of the milk are made. Plates of whey agar are inoculated with these different dilutions of the milk. Colonies of Bacillus Acidophilus in agar are so minute that they are observable with difficulty, except with the aid of a powerful lens or microscope. The microscopical examination of these developed agar plates determines the purity of the culture and the number of organisms per cubic centimeter.



Only Milk from Clean, Healthy Cows Is Used in the Manufacture of Bacillus Acidophilus Milk (Lederle)

Bacillus Acidophilus Milk (Lederle) differs from "Beverage Sour Milks"

Far more detailed equipment and greater technical skill are necessary to safeguard Bacillus Acidophilus Milk (Lederle) than is required in the preparation of Bacillus bulgaricus milk or other "beverage sour milks" in common use. This is explained by the fact that the Bacillus Acidophilus is slow-growing as compared with organisms which usually contaminate milk; and if milk containing other organisms (native or pasteurized milk) is inoculated with even comparatively large volumes of the most active cultures of Bacillus Acidophilus, the more rapid growth of the contaminating organisms will overgrow the Bacillus Acidophilus so that the resultant product will be unfit for use. For this reason a safe preparation of Bacillus Acidophilus Milk can be made only where there are complete facilities for bacteriological control of the product in every step of its manufacture from the preparation of the seed culture to the bottling of the finished product.

Quality of Milk

The milk used in the manufacture of Bacillus Acidophilus Milk (Lederle) is pure WHOLE milk obtained from clean, healthy cows. Much of the milk used to make the beverage sour milks is skim milk that has become highly contaminated before being processed.

Warning

Since Bacillus Acidophilus Milk (Lederle) was introduced to the medical profession, there have been offered in various parts of the country, locally-prepared milks that are sold as Bacillus Acidophilus Milk but which in reality contain little, if any, Bacillus Acidophilus. We have examined in our laboratory a number of these products and found many to contain a variety of organisms with the Bacillus bulgaricus mainly predominating. This organism so closely resembles the Bacillus Acidophilus that with the equipment ordinarily available to the practicing physician, this organism could not be differentiated from the Bacillus Acidophilus. This practice cannot fail to produce disappointing results.

Physicians who are desirous of employing Bacillus Acidophilus Milk prepared according to the standard established by Professor Rettger of Yale University, should make sure that their patients use a "Council Passed" Bacillus Acidophilus Milk. They should be cautious with regard to the use of any acidophilus milk not passed by the Council on Pharmacy and Chemistry of the American Medical Association.

Influence of Thyroid Substances on Absorption of Plural Effusions

DURING the course of pneumonia, pleural effusions develop in many patients. Some of these effusions are small and are absorbed soon after the crisis; others are large and last for several weeks and are accompanied by fever and prolonged convalescence.

Experimental investigations by Eppinger showed that there was a striking difference between the absorption of subcutaneous fluid from normal and from thyroidectomized animals. In normal animals, considerable amounts of saline solution were absorbed from the skin; but

saline thus injected into animals deprived of the thyroid gland was not absorbed. In such animals, a subcutaneous edema was produced. These results indicate the governing influence of the thyroid secretion on the water transport from the subcutaneous tissues. EPPINGER reasoned that mild forms of hypothyroidism might remain latent until some edema factor, like heart or kidney insufficiency, was super-added. The edema would then be out of all proportions and clinical improvement would follow only when thyroid was administered.

Based on these experiments of EPPINGER, it seemed plausible that such an explanation would account for the pleural effusions in pneumonia; for pneumonia in a person with a tendency to edema (latent hypothyroidism) may cause an extensive pleural effusion or edema.

With this as a background, DENZER at the City Hospital in New York City administered thyroid substances to four patients suffering with pleural effusion. Three of these cases were associated with pneumonia, while one was primary and probably due to pulmonary tuberculosis. Thyroid substance was given every four hours for one week.

The three cases of pleural effusion associated with pneumonia showed a distinct tendency to rapid absorption. There was a striking diminution in the amount of fluid after three days, and at the end of one week the fluid was gone. This was demonstrated both by physical and X-ray examination. The one case of primary pleural effusion, probably tubercular in nature, was not affected by the thyroid administration.

In view of the decisive results obtained, even in this small series of cases, it would seem that this method of treating pleural effusions that occur during the course of pneumonia was well worth a more extensive trial.

Scarlet Fever Antitoxin

DURING the present year, rapid progress has been made in the scientific study of scarlet fever. As a result, the outlook for a more efficient control of this disease is more promising than ever before.

Among the outstanding contribu-

tions in the recent investigation of scarlet fever are those of DICK and DICK of the John McCormick Institute for Infectious Diseases in Chicago. After working many years in this field, these investigators have isolated strains of hemolytic streptococci which apparently have fulfilled all the requirements of KOCH's law, even to that of producing scarlet fever in human volunteers. They have shown that the scarlet fever streptococci produce a toxin which, when injected into susceptible persons, causes nausea, vomiting, malaise, fever and a scarlatinal rash. This toxin gives a skin test for susceptibility to scarlet fever and can be used in preventive immunization.

A horse has been immunized with this toxin, and it was found that 10 cc of his serum contained antitoxin sufficient to neutralize twenty times the amount of toxin that produced nausea, fever and a scarlatinal rash in susceptible persons. After the serum had been subjected to the concentration process, tests showed that the antitoxin had not been destroyed or lost in the process.

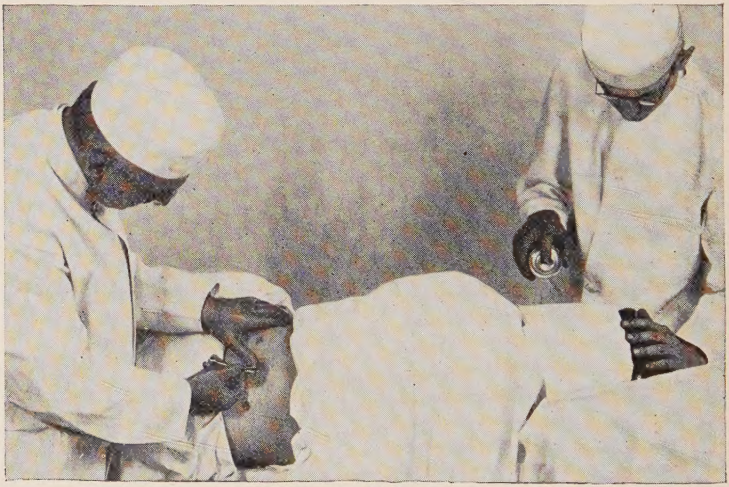
The therapeutic value of the scarlet fever antitoxin has been thoroughly demonstrated by several workers, and this product seems destined to come into general use as a valuable means of treating scarlet fever.

The Rational Treatment of Tetanus

THE prognosis of tetanus treated without antitoxin has been exceedingly unfavorable, the mortality being estimated at 74 to 80 per cent. Most fatal cases die within the first six days, and cases living to the sixth day are very much more apt to get well. The late-appearing cases of tetanus, in which symptoms first occur ten or more days after the injury, give the most favorable prognosis. And cases of "delayed tetanus," which occur after the immunizing effect of the prophylactic dose of antitoxin has disappeared, also have a good prognosis.

When treatment with antitoxin administered by the INTRASPINAL method was employed promptly after the recognition of tetanus symptoms, PARK obtained recoveries in 50 to 80 per cent of the cases. *The early administration by the intraspinal route* of large doses of Tetanus Antitoxin is essential for the success-

ful treatment of a case of tetanus; because, after tetanus toxin up to a certain amount which constitutes the "fatal limit" has combined with the cells of the central nervous system, no amount of Tetanus Antitoxin can



MAKING A LUMBAR PUNCTURE

The point for inserting the needle is between the 3rd and 4th lumbar vertebrae and a little to one side of the median line, the thumb of the left hand being placed between the spinous processess as a guide. This point is about on a level with the highest point of the iliac crests, here shown by two small spots of iodin. The operation is performed under an anesthetic, such as chloroform, and the patient is placed on the side with knees drawn up and head bent forward so as to arch the back and thus widen the interarticular spaces. The skin in the lumbar region is painted with iodin.

save the life of the patient.

The pioneer work of PARK and NICOLL, together with the extensive experience gained in the World War, has proven that the INTRASPINAL METHOD of administering Tetanus Antitoxin should be given preference over all other methods. *The intraspinal injection of antitoxin, warmed to body temperature (98.6° F.), should be given slowly by gravity and always, if possible, under an anesthetic such as chloroform.*

The technic of intraspinal administration includes making a lumbar puncture between the third and

fourth lumbar vertebrae and withdrawing cerebrospinal fluid. The fluid should be allowed to flow until the cerebrospinal fluid pressure falls to normal: one drop from the needle every three to five seconds being about normal. In case of a "dry tap" which has been reported on good authority as occasionally occurring in tetanus, the intraspinal injection of antitoxin should be given cautiously.

Withdrawing Cerebrospinal Fluid

As soon as the dura has been punctured, the stylet is withdrawn from the needle and the cerebrospinal fluid allowed to flow until the cerebrospinal fluid pressure falls to normal: one drop from the needle every three to five seconds being about normal.

The following dosage is recommended for the complete antitoxin treatment of all cases of tetanus:

First Day

5,000 to 10,000 units intraspinally
10,000 units *intravenously*

Second Day

5,000 to 10,000 units intraspinally

Third Day

5,000 units intraspinally

FOURTH DAY

5,000 to 10,000 units *subcutaneously*

When this recommended dosage and method of treatment is followed, improvement is usually manifested in 48 hours after the first intraspinal injection; and the improvement becomes progressive. However, the trismus and rigidity will persist after the above mentioned antitoxin treatment has been completed, but these symptoms will gradually improve without further administration of antitoxin.

If, for any reason, Tetanus Antitoxin cannot be given immediately in the spinal canal, it is advisable to inject 20,000 units intravenously; and in case it should also be impossible to make an intravenous injection, 30,000 units should be injected intramuscularly using several muscles.

INTRASPINAL INJECTION OF ANTITOXIN

After the cerebrospinal fluid has been withdrawn, the glass cylinder is attached by rubber tubing to the needle which is left in position; and the antitoxin, warmed to body temperature, is allowed to flow into the spinal cavity by gravity.

However, no amount of antitoxin

administered by any other than the intraspinal route will as surely protect the nervous system from a fatal amount of tetanus toxin. *Therefore, arrangements should immediately be made for giving an intraspinal dose at the earliest possible moment.*

Supplemental Treatment

In addition to the antitoxin treatment, proper surgical treatment to the wound should be applied and the patient placed in a quiet, darkened room with competent nursing facilities. The patient should be protected as carefully as possible from noise, excessive light, draft, jars and other forms of irritation. In case the wound has not been given thorough surgical cleansing, it ought to be widely opened by free incision to thoroughly cleanse it and to remove foreign substances. It is recommended that the wound be irrigated with hot peroxide of hydrogen, then swabbed out with 3 per cent alcoholic solution of iodin and loosely packed with gauze soaked in the same solution.

The convulsions should be controlled by *sedatives,* such as chloral hydrate which is well borne in tetanus cases. Many patients experience great relief from *warm baths* twice daily which have a decided calming effect and also tend to diminish the trismus. An adequate supply of *fluid nourishment* should be given, and careful attention paid to *elimination by the kidneys and bowels.*

Bacillus Acidolphilis Milk and its Therapeutic Effects

WITH the object of extending their clinical observations on the therapeutic value of the oral administration of viable milk cultures of Bacillus Acidophilus, Cheplin, Post and Wiseman carried out a clinical study of nine cases. This group of patients suffered from such conditions as mucous colitis, constipation and diarrhea.

Bacteriological examinations of the stools of each patient were made before treatment and again at intervals of one to three weeks. These fecal examinations were made to determine the progress in the transformation of the intestinal flora from the mixed type to one dominated by Bacillus Acidophilus.

The results of this investigation

show (1) that Bacillus Acidophilus Milk possesses therapeutic properties in the treatment of these intestinal conditions; (2) that Bacillus Acidophilus can be successfully implanted in the human intestine; and (3) that the colonization of the Bacillus Acidophilus as a predominating organism in the intestine can be maintained as long as the oral administration of the milk culture in proper amounts continues.

The therapeutic value of Bacillus Acidophilus depends on its ability to suppress B. coli and on its inhibiting effect upon B. welchii, B. proteus, B. putrificus and other undesirable toxicogenic intestinal bacteria. The authors believe that the transformation of the intestinal flora by means of Bacillus Acidophilus Milk minimizes autointoxication and is indicated in the so-called toxic intestinal conditions.

In constipation, Bacillus Acidophilus Milk produces beneficial results by regulating the bowel movements, while in diarrhea and mucous colitis its effects are shown by a gradual restoration of formed movements and the disappearance of mucus. Coincident with these changes, there is a relief from toxic symptoms which previously existed. These improved conditions bear a definite and constant relationship to the change in the intestinal flora. During the course of these studies, none of the constipated patients fail to show some relief from constipation and clinical symptoms, as a result of an intensive course of treatment with Bacillus Acidophilus Milk.

The authors sound a word of warning by pointing out that Bacillus Acidophilus Milk therapy is not a cure for all kinds of ailments, stating that all cases of gastrointestinal disturbances will not necessarily respond to this treatment. It is not an elixir nor a so-called "longevity bug" in the sense that Bacillus bulgaricus was once hailed. They emphasize the fact that the ingestion of relatively few acidophilus bacilli will not lead to implantation nor to bodily improvement. They advocate the daily administration of 500 or preferably 1,000 cc of fresh milk culture of Bacillus Acidophilus for a period of at least six weeks or longer to produce clinical improvement.

Attention is directed to the fact that tests conducted by the authors confirm the observation of Bass to the effect that tablets containing Bacillus Acidophilus are of no value whatever in transforming the flora and relieving the symptoms. There-

fore, they strongly advocate the adoption of Bacillus Acidophilus Milk as the surest and most effective means of attaining the desired results in the various intestinal conditions mentioned.

The Dreyer Tuberculosis Antigen

Experiments Conducted in the Lederle Antitoxin Laboratories

EVER since the report last year of the researches reported by Professor GEORGES DREYER of the Department of Pathology in Oxford University, England, the medical world has been keenly interested in the possibility of this product proving to be of value in the treatment of tuberculosis.

As stated in an editorial of *The Journal of Laboratory and Clinical Medicine:*

> "Dreyer argues that, in general, better immune responses are found after inoculation of Gram-negative and nonacid-fast bacteria than can be determined after inoculation with Gram-positive and acid-fast organisms. The condition of acid-fastness and Gram-positiveness are associated with the presence in the bacterium of certain waxy, fatty or lipoid substances. These are generally referred to as 'lipoidal substances.' Such substances protect the specific bacterial proteins and so enable the bacteria to resist tryptic digestion and prevent, following inoculation, the 'liberation from the body of the bacterium of the sole adequate stimulus for the immunity reaction of the infected organism.' "

DREYER'S method not only removes the lipoidal substances but also renders the organisms Gram-negative and non-acid-fast. As previously pointed out in this *Bulletin,* the method devised by DREYER embraces the use of formaldehyde and acetone.

DREYER described in detail experiments on four guinea-pigs which were infected with a living culture of the tubercle bacillus of the human type but of *low virulence;* animals infected with it dying usually in 6 or 8 months after infection. Treatment consisted in ten injections of "defatted" antigen at intervals of 3 to 13 days and consumed a period of 18 weeks. Experiments were also made on four rabbits, three being treated with the defatted tubercle antigen while the fourth served as

a control. These animals were inoculated with living bovine tubercle bacilli, the virulence of the culture being sufficient to kill the control animal in about four months. The results in all of the animals treated with the antigen appeared to indicate arrest of the disease.

Obviously, these experiments were entirely too few and were conducted over too short a period of time to justify any dogmatic statement concerning the possible value of the DREYER antigen. However, the experiments of DREYER seemed to be suggestive of a possibility of an improved product for tuberculosis therapy. Therefore, it was deemed worth while to determine in a more comprehensive and decisive manner the actual value of the antigen.

EXPERIMENTS CONDUCTED IN LEDERLE ANTITOXIN LABORATORIES

With this aim in view, an extensive series of experiments was conducted in the LEDERLE ANTITOXIN LABORATORIES, and a larger number of animals was used to make possible a more definite conclusion regarding the value of the antigen. A quantity of the DREYER antigen was made, using the methods described by Professor DREYER. Some of this was distributed for clinical trial among tuberculosis sanatoria in this country and to physicians who have made a special study of tuberculosis; the balance of the antigen being used for our animal experiments.

The susceptibility of the guinea-pig to the tubercle bacillus is well known; hence, these animals were chosen for the tests. A total of 110 guinea-pigs was inoculated at one time with a living culture of tubercle bacilli of the human type, having a virulence such that infected animals die usually in 5 to 6 weeks. Of this number, 50 were used as controls; 30 of these receiving no treatment and 20 being given Tuberculin "B. E." (Bacillary Emulsion). The remaining 60 inoculated guinea-pigs were treated with the DREYER antigen.

Treatment with the DREYER antigen and with the Tuberculin "B. E." was started 7 days after the animals were inoculated with the living culture of the tubercle bacilli. Doses of 1 cc of Tuberculin "B. E." were administered at weekly intervals to the series of 20 guinea-pigs, while the 60 animals which were treated with the Dreyer antigen were divided into three groups of 20 each; one group receiving ½ cc of the antigen at weekly intervals; the second group being given 1 cc at the same

TABLE I

Showing General Summary of Results of Animal Experiments Conducted in the Lederle Antitoxin Laboratories

Treatment	Total No. Guinea-pigs on Test	Results at the end of							
		2½ months		3½ months		5½ months		6½ months	
		Dead	%	Dead	%	Dead	%	Dead	%
DREYER Antigen	60*	5	8	21	35	52	86	56	93
Controls: Tuberculin "B. E."	20	10	50	12	60	18	90	19	95
Controls: Untreated	30	13	43	20	66	26	86	29	96

*Details of the result of treatment of these 60 guinea-pigs is given in Table II.

intervals, while the third group received at weekly intervals 2 cc of the antigen. Whenever death occurred in any of the guinea-pigs, a complete autopsy was made with special search for tubercle lesions. With the exception of four guinea-pigs on which autopsy findings showed positive lesions of pneumonia, all animals which died during the experiment showed typical pathological lesions of diffuse tuberculosis.

Results of Experiments

The accompanying tables show the results of the experiments at different intervals as well as the final results. These animal experiments indicate that the Dreyer antigen was in no sense a cure for tuberculosis in these guinea-pigs, yet the fatal outcome in those guinea-pigs treated with the Dreyer antigen was unquestionably delayed. This is illustrated in Table I. During the early months of experiments, the percentage of animals that died under the treatment with Dreyer antigen was very low as compared to the number of untreated guinea-pigs or even those treated with Tuberculin "B. E." This shows that the antigen did protect the animals for a time against the ravages of the disease.

TABLE II

Detailed Results of Treatment with the DREYER Antigen (Animal Experiments Conducted in the LEDERLE ANTITOXIN LABORATORIES)

Treatment	Dose of Antigen	Number of Animals on Test	Results at the end of							
			2½ mos.		3½ mos.		5½ mos.		6½ mos.	
			Dead	%	Dead	%	Dead	%	Dead	%
DREYER Antigen	½ cc	20	All	living	2	10	14	70	17	85
DREYER Antigen	1 cc	20	2	10	6	30	19	95	19	95
DREYER Antigen	2 cc	20	3	15	13	65	19	95	20	100

Another point which these experiments have emphasized is that Tuberculin "B. E." possessed practically no protective power against guinea-pig tuberculosis. The percentage of animals dead under Tuberculin "B. E." treatment at varying intervals of the experiments was substantially the same as the percentage of untreated guinea-pigs.

Still another fact brought out by these experiments is illustrated in Table II. And that is, that small doses of the DREYER antigen apparently gave better protection than did the large doses.

The results of the series of experiments conducted in the LEDERLE ANTITOXIN LABORATORIES indicate that this product may be an important advance in the treatment of tuberculosis. One point worthy of mention is that while an infective culture of the tubercle bacillus killed guinea-pigs in these experiments within two months, the normal course of tuberculosis in human beings often extends over a period of years. Therefore, in view of the fact that some protection against tuberculosis was shown in the guinea-pigs used in these experiments, there is a much more favorable opportunity in the human subject for a longer treatment with the antigen which

should stimulate a greater degree of protection. Only the experience gained from the use of the DREYER antigen over a long period can determine its actual value as a therapeutic agent.

Vaccination by the Oral Route

IN experimental studies of immunity, BESREDKA found that local immunization is a factor hitherto accorded comparatively little consideration. He believes that the mechanism of vaccination against intestinal diseases is the same, whether the vaccine is administered by mouth or by hypodermic injection into the subcutaneous tissue.

In all of the so-called intestinal diseases, such as typhoid and paratyphoid fevers, cholera, dysentery, etc., the receptive organ is the intestine. BESREDKA believes that ox bile intensifies normal biliary secretion; increases the intestinal peristaltic movements; removes the layer of mucus, and thus brings about a preliminary cleansing of the intestine which allows the receptive cells to come in direct contact with the vaccine when administered orally.

In recent years, a large number of oral vaccinations against typhoid and paratyphoid fever have been conducted, and their harmlessness has been definitely established. These vaccinations have been carried out in persons presenting definite contraindications to subcutaneous vaccination. So far as the efficiency of the oral vaccination is concerned, sufficient time has not yet elapsed to form a definite opinion. Large groups of people in the civil as well as military population have been vaccinated by the oral route during epidemics, and thus far the results appear to be favorable. In a town having a population of 2,000, among the 600 who were not vaccinated, 50 contracted typhoid fever or 7.7 per cent. Out of the 173 that had been vaccinated subcutaneously, four developed the disease or 2.3 per cent. Of the 1,236 inhabitants who took the bile vaccine by mouth 5 developed typhoid fever or 0.17 per cent. BESREDKA believes that the oral method produces an immunity which is at least equivalent, if not superior, to that attained by the subcutaneous method.

NICOLLE and CONSEIL conducted similar experiments with Malta fever

and dysentery. Their experiments demonstrated that it is possible to immunize against these two diseases when the vaccine is administered by the oral route.

While all of these experiments are entirely too few to permit of the formulation of a definite conclusion or recommendation concerning the value of vaccination by the oral route, yet they are extremely interesting from a scientific standpoint and worthy of being closely followed. If this method proves to be all that BESREDKA claims for it, the problem of vaccinating people against typhoid fever and other diseases may be very greatly simplified; for many people who look askance at hypodermic injection will readily submit to taking a pill.

Clinical Value of Bacillus Acidophilus Milk

AT the suggestion of one of the members of the National Research Council, and with the permission of Professor RETTGER of Yale University, CLARK and PERRY conducted an investigation extending over eighteen months into the clinical value of Bacillus Acidophilus Milk in gastro-intestinal disorders. They have reported observations on 84 patients.

CONSTIPATION

Fifty patients with chronic constipation were treated with Bacillus Acidophilus Milk over a six weeks' period. The constipation in these patients had persisted for many years. All of the patients had been taking some laxitive routinely every day. The results in general showed that Bacillus Acidophilus Milk with lactose has a distinctly laxative effect. Moreover, the authors are of the opinion that such symptoms as debility, lassitude and depression, which are commonly attributed to constipation or autointoxication were markedly improved coincident with the correction of constipation.

INTESTINAL GAS

Especially benefited were those patients who had complained of an excess of intestinal gas, of flatulence, and of the passage of large amounts of gas by rectum. A majority of these comprised those in the constipation group, although eight cases were included in which constipation was not present. This group of pa-

tients complained of such symptoms as a sense of fullness, of heaviness, of shifting abdominal pain, so-called "gas pain," and of explosive passage of gas. Drowsiness, lethargy and a tired feeling were also common symptoms in this group. Of the 27 patients complaining of excessive intestinal gas, 23 reported marked improvement after treatment with Bacillus Acidophilus Milk and 4 noted no effect. No patient in this series reported an increase of symptoms.

Functional Indigestion

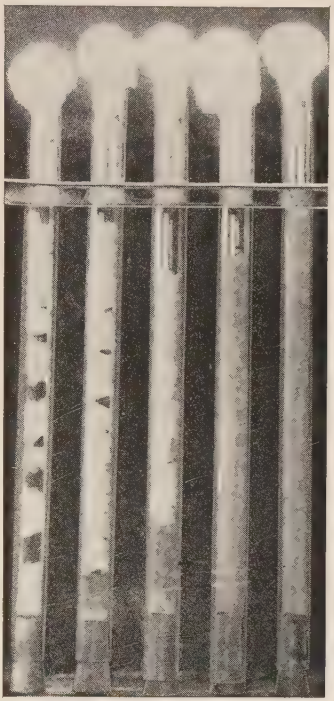
Five elderly patients between 65 and 70 years of age, who had chronic myocardial weakness, suffered with intestinal gas and bloating. Relief from the digestive disturbance was marked in all five cases under Bacillus Acidophilus Milk treatment.

Chronic Diarrhea

A group of 6 cases of chronic diarrhea were studied, the duration of the condition ranging from one month to six years. All of these patients made a rapid recovery under acidophilus milk therapy and have remained well at the end of one year.

Sprue

One case of tropical sprue which had lasted for two years made a rapid and complete recovery under



Courtesy of Prof. Rettger, Yale Univ.

Veillon tubes used in determining gas-producing organisms in the intestine. Note the gradual diminution of gas production from left to right. The gradations correspond to the different stages of transformation of the usual complex flora to the simple flora dominated by *Bacillus Acidophilus;* the last tube showing complete absence of gas.

acidophilus milk therapy. At the end of one year, the patient continued in normal health. In the opinion of CLARK and PERRY, the Bacillus Acidophilus Milk was responsible for the good result in this case and they feel that this form of treatment could well be investigated by those treating a large number of cases of tropical sprue.

CHRONIC ECZEMA

Four cases of chronic eczema due to toxic intestinal absorption were given the Bacillus Acidophilus Milk treatment. The skin condition in three patients cleared up under this treatment, while one showed no improvement.

LABORATORY STUDIES

CLARK and PERRY did not attempt to carry out extensive bacteriological studies on the stools of the patients before and after the use of the acidophilus milk. However, in the few cases in which such examinations were satisfactorily completed, their findings coincided with those of RETTGER and his co-workers at Yale University. They found that the transformation from a Gram-negative flora to one that was preponderatingly Gram-positive, was very striking.

As a rule, the taste of the milk proved acceptable to all of the patients, most of them stating that they liked the milk. It has a mildly acid flavor and is ideal as a food. All patients, except the group of six with chronic diarrhea, were on an ordinary well-balanced diet.

Results Obtained with the Dick Test in Scarlet Fever

AT the Willard Parker Hospital in New York, ZINGHER has found that the DICK test is positive as a rule during the first two days of scarlet fever, but becomes negative toward the end of ten to fifteen days when the antitoxic properties begin to appear in the patient's serum. The antitoxic properties can be shown by the power of the serum to blanch the scarlet fever rash and to neutralize the scarlet fever toxin.

ZINGHER applied the DICK test in a series of 100 cases of scarlet fever during the first four days of the disease and found them to be positive in all but three. As the patients progressed into convalescence, they nearly always showed a negative reaction. ZINGHER has now used the DICK test in more than 7,000 school children and has demonstrated its practical value.

At the present time, the standardization of the scarlet fever toxin is most satisfactorily carried out by testing it intradermally in different dilutions (usually 1:500 to 1:2,000) in susceptible individuals. Of this diluted toxin, 0.1 cc is injected intradermally in the forearm and should produce a positive reaction. This amount of toxin represents one skin test dose. The positive reaction appears within 6 to 12 hours, reaches its height at the end of 24 hours and rapidly fades; and is followed by pigmentation which may persist for a week or longer.

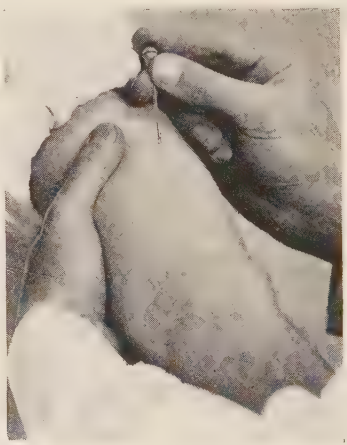
ZINGHER states that the neutralization of the scarlet fever toxin is a more delicate index of the presence of antibodies in the scarlet fever antitoxic serum than is its property to cause blanching of a scarlet fever rash. The standardization of the antitoxin is determined by mixing equal volumes of double strength toxin (twice the strength used in the DICK test) with increasing dilutions of the antitoxin (usually 1:50, 1:25 and 1:10) and then injecting 0.5 cc of these mixtures into an individual who has previously shown a good positive Dick reaction.

ZINGHER believes that the DICK test is of great value and will find an increasing field of application in the selection of susceptible persons for passive and active immunization: for passive immunization with scarlet fever antitoxin serum, and for active immunization with increasing doses of the scarlet fever toxin. A negative re-test after active immunization would indicate the development of antitoxic immunity; but such re-tests should not be made until two or three months after active immunization.

Studies in active immunization with diluted scarlet fever toxin have shown that immunization by this method is a practical procedure. For this purpose, ZINGHER uses three doses administered subcutaneously at intervals of one week; the volume of each dose being one cubic centimeter. The prophylactic treatment now being used by ZINGHER comprises 100, 250 and 500 skin test doses. Active immunization with diluted scarlet fever toxin has been extensively applied—about 1,000 such immunizations having been given in various institutions in New York City—and the results have proved to be uniformly satisfactory. This method of protecting against scarlet fever is destined to be widely used; for through its application, the prevention of scarlet fever is now possible.

Vaccination Against Smallpox

IN the United States, well-vaccinated communities show low smallpox rates. Poorly-vaccinated States tell another story: Oregon with 1.45 per thousand population, Washington with 1.72 and Kansas with 2.0 per thousand population. Some communities wait till an epidemic breaks out and then rush to vaccinate. This stops the disease—after it has caused many deaths and "branded" many survivors. Such epidemics as have recently occurred in Kansas City, Denver, Columbus and Detroit, always end the opposition to vaccination in the community—for a time. Thorough and systematic vaccination will eliminate the scourge of smallpox from every locality. The United States Public Health Service recommends vaccination in infancy, again at school age, in early adult life and whenever smallpox threatens to become epidemic. Successful re-vaccination is just as important as a successful first vaccination.



EXPELLING VACCINE VIRUS FROM CAPILLARY TUBE ONTO CLEANSED SKIN

KEEP VACCINE VIRUS COLD

The expiration date on a package of Vaccine Virus indicates its expectancy of potency under favorable conditions. Vaccine Virus cannot be kept too cold; it deteriorates rapidly even at room temperature. The freshest possible vaccine should be used, and this can be done by arranging for small and frequent shipments. During the summer months, special attention must be given to the storage and shipping of Vaccine Virus; for if its vitality has at any time been

weakened by improper storage or handling, subsequent storage on ice will not restore the usefulness of the product.

The Vaccination

The original vaccination wound should be made as small as possible to guard against infection. Years of experience has proved that the correct way to make a vaccination against smallpox is by using a steel needle point, and the most approved location is the upper arm in the region of the insertion of the deltoid muscle. The skin should be thoroughly cleansed with acetone or ether on sterile gauze. After evaporation of the acetone or ether, place a drop of Vaccine Virus upon the cleansed skin by expelling the virus from the glass capillary tube by compressing the rubber bulb.

Making Multiple Punctures with Needle Point Pressed Through Drop of Virus

Multiple Puncture Method

Vaccination should never be performed by cross scratching.

To secure the best results, the following procedure is recommended: With the left hand, grasp the under surface of the arm in order to stretch the skin where the virus has been placed. With the right hand holding new sterile needle parallel with the skin, make about six oblique pricks or shallow punctures through the epidermis by pressing the point of the needle through the drop of virus. *Confine the punctures to an area not more than one-eighth (⅛) of an inch in diameter.* Sufficient virus to produce a satisfactory "take" or vaccination will be carried beneath the superficial layers of epidermis by these multiple punctures. The surplus virus on the surface of the skin should be wiped off immediately with sterile gauze, using

a single stroke. NO SHIELD or other dressing should be applied. The vaccination site should not be exposed to direct sunlight for four hours.

Advantages of Puncture Method

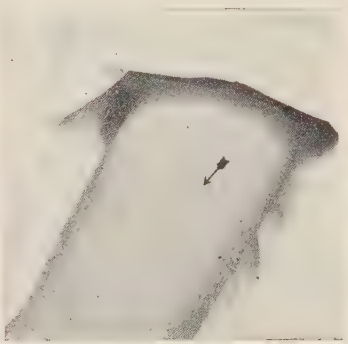
1. Virus may be wiped off immediately after vaccination; no waiting for wound to dry before clothing touches it.

2. Least painful of any method.

3. Leaves practically no scar—hence, is an added advantage when vaccinating girls.

4. Insures greatest freedom from sore arms and infection.

5. Safest procedure in vaccinating infants and small children.



Arrow Points to Scar, Almost Invisible, Resulting from Multiple Puncture Method of Vaccination

Reactions

(A) If the person has not been previously immunized, the reaction will appear as a primary "take" or vaccinia. On the third or fourth day after vaccination, a papule appears which becomes vesiculated on the next day and is surrounded by a red margin or areola which rapidly extends to a wide area about the seventh or eighth day. The maximum size of the vesicle and area is reached on or about the ninth or tenth day, after which the area rapidly fades and the vesicle becomes brown and crusted. If kept dry, the crust will separate in approximately three weeks from the day of vaccination.

(B) If the person retains some degree of immunity, either from previous vaccination or an attack of smallpox, the reaction will appear sooner and last a shorter time. Such a reaction is termed a "vaccinoid," or accelerated reaction.

(C) If the immunity is very high, the acceleration may be so great that the reaction consists only of a papule with areola *reaching its maximum size in 12 to 60 hours after*

vaccination. Under such conditions no vesicle usually forms, and the reaction is termed "immunity reaction" or immediate reaction.

If the vaccine has been properly kept and applied, one of these three forms of "take" will appear in every case. If none of these reactions occur, it does not indicate that the subject is immune but rather that the virus is inactive and worthless and is therefore incapable of protecting against smallpox.

Prophylaxis of Chicken-pox with Convalescent Serum

AT the Department of Pediatrics of Johns Hopkins University, WELCH has recently applied to chicken-pox the method of using convalescent serum as a prophylactic measure, in much the same way that convalescent serum of measles has been so successfully used. He tested this method of prophylaxis in nine infants.

In hospital practice where the long incubation period necessitates keeping a ward under quarantine for over three weeks, any method of lessening the quarantine period and preventing the occurrence of secondary cases is of value.

The serum was obtained from children from ten to twenty days after the first appearance of the rash. From 3 to 4.5 cc of the serum was injected intramuscularly into nine infants within one to six days after exposure. Eight of them did not contract the disease. In the ninth infant, an extremely mild attack developed after an unusually long incubation period (22 days).

Under ordinary circumstances, as pointed out by WELCH, an attack of chicken-pox is so mild and the sequelae so few that prophylaxis has not been considered of great importance. His report is, nevertheless, very interesting for it is evidence of the trend of modern medicine to follow along preventive lines.

Efficiency in the Treatment of Diphtheria with Antitoxin

MADSEN at Copenhagen has reported that by the use of very large doses of antitoxin up to 200,000 units per patient, the mortality from diphtheria was cut down to 1.2%. Moreover such large amounts of antitoxin did not produce more serum sickness than the smaller amounts usually used.

In recent years the New York City Department of Health under the supervision of PARK has made extended studies relative to the most effective way of administering antitoxin and it has been proven that by the proper route of administering, antitoxin in much smaller doses will give even better results.

Attention is therefore specially called to the method of administration of antitoxin. The following is quoted from recommendations of the New York City Department of Health:

"It is recommended that the methods of administration be as follows:

Mild Cases—Subcutaneous or intramuscular.

Moderate Cases—Intramuscular or subcutaneous.

Severe Cases—Intravenous or intramuscular.

Malignant Cases—Intravenous."

If this method of administration is followed, deaths from diphtheria may be kept to a minimum without the enormous dosage used by MADSEN. We suggest the dosage as recommended in the following table and lay special emphasis on the prompt injection of the entire amount of antitoxin in one dose.

Dosage Table for Diphtheria Antitoxin

All the Antitoxin intended for the entire treatment of the case should be given as early as possible and IN ONE DOSE.

Type of Case	Dose in Units	Method of Administration
Mild-treated on the first day	5,000 (3,000 in infants under 20 lbs.)	Intramuscularly
Mild-treated on the second day or later Moderate-treated on the first day	10,000	Intramuscularly
Moderate-treated on the second day or later Severe-treated on the first day	*10,000 to 20,000	Intravenously
Severe-treated on the second day or later Malignant including combined pharyngeal and laryngeal	*20,000 to 50,000 (10,000 in infants under 20 lbs.)	*Intravenously

*If for any reason the intravenous method can not be used, double the amount should be given intramuscularly.

Prevent Rabies

with

Canine Rabies Vaccine *Lederle*

(One Injection Method)

RABIES has not developed, even by direct vaccination, in a dog within one year of its immunization with Canine Rabies Vaccine Lederle (*One Injection Method*).

This product has been used on many thousands of dogs to prevent the development of rabies. A single failure has not been reported.

Canine Rabies Vaccine (*One Injection Method*) is a product introduced in America by the LEDERLE ANTITOXIN LABORATORIES in August, 1921, based upon the extensive researches of Drs. Eichhorn and Lyon following the investigations in Japan.

Its Universal Application to All Dogs Will Eliminate Rabies

Protect the Boy

by immunizing his pet and companion against rabies

The time usually elapsing between the "bite" and symptoms is from 12 days to 3 months, but may be as long as one year. After symptoms have developed, treatment is absolutely useless, for there is no known cure.

Canine Rabies Vaccine *Lederle*

is supplied in 5 cc vials. A tag for the immunized dog is enclosed in each package.

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Tetanus Antitoxin

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(Refined and Concentrated)

PACKAGES

1500 units in syringe
5000 units in syringe
5000 units (Intraspinal)
10000 units (Intravenous)
10000 units in syringe
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Tuberculin "O. T." is supplied in packages (Dilution "C" Tuberculin "O. T.") sufficient for about ten tests.

Full details upon request

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Toxin Antitoxin

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For Immunization Against Diphtheria

PARK conclusively demonstrated the value of diphtheria immunization with Toxin-Antitoxin Mixture. Immunity still persists in over 90% of children immunized six years ago.

Toxin Antitoxin (Lederle) is made according to PARK's modified formula, containing one-tenth L plus dose of toxin.

Studies during the past two years show that no severe reactions followed the use of this modified formula either in children or adults. This product therefore permits of universal immunization against diphtheria.

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may be obtained through your druggist or will be sent direct to your patients upon order.

Packages containing six 8-ounce bottles, $1.75
Packages containing three 1-qt. bottles 2.50

Plus transportation charges from New York.

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